Claims

1. A modified adenoviral fiber containing at least one mutation affecting one or more amino acid residue(s) of said adenoviral fiber interacting with at least one glycosaminoglycan and/or sialic acid-containing cellular receptor.
2. The modified adenoviral fiber according to claim 1, wherein said modified adenoviral fiber has an affinity for said glycosaminoglycan or sialic acid-containing cellular receptor of at least about one order of magnitude less than a wild-type adenoviral fiber.
3. The modified adenoviral fiber according to claim 1 or 2, wherein said glycosaminoglycan-containing cellular receptor is a heparin- or heparan sulfate-containing cellular receptor.
4. The modified adenoviral fiber according to claim 3, wherein said heparin- or heparan sulfate-containing cellular receptor is a heparan sulfate glycosaminoglycan (HSG) cellular receptor which normally interacts with the wild-type adenoviral fiber to mediate adenovirus attachment to a host cell.
5. The modified adenoviral fiber according to any one of claims 1 to 4, wherein said mutation affects one or more amino acid residue(s) within the AB loop, the CD loop, the DG loop and/or the beta sheet I of the knob.
6. The modified adenoviral fiber according to any one of claims 1 to 5, wherein said mutation affects one or more amino acid residue(s) selected from the group of residues consisting of the threonine in position 404, the alanine in position 406, the valine in position 452, the lysine in position 506, the histidine in position 508, and the serine in position 555 of the wild type Ad5 fiber protein as shown in SEQ ID NO : 1.
7. The modified adenoviral fiber according to claim 6, wherein said mutation comprises :
   - The substitution of the threonine in position 404 by glycine,
   - The substitution of the alanine in position 406 by lysine,
   - The substitution of the valine in position 452 by lysine,
   - The substitution of the lysine in position 506 by glutamine,
   - The substitution of the histidine in position 508 by lysine, or
   - The substitution of the serine in position 555 by lysine,
   - Or any combination thereof.
8. The modified adenoviral fiber according to claim 6 or 7, wherein said mutation comprises :
   - the substitution of the lysine in position 506 by glutamine and the substitution of the histidine in position 508 by lysine ;

- the substitution of the threonine in position 404 by glycine, the substitution of the lysine in position 506 by glutamine and the substitution of the histidine in position 508 by lysine ;
- the substitution of the alanine in position 406 by lysine, the substitution of the lysine in position 506 by glutamine and the substitution of the histidine in position 508 by lysine ;
- the substitution of the valine in position 452 by lysine, the substitution of the lysine in position 506 by glutamine and the substitution of the histidine in position 508 by lysine ;
- the substitution of the lysine in position 506 by glutamine, the substitution of the histidine in position 508 by lysine and the substitution of the serine in position 555 by lysine.

9. The modified adenoviral fiber according to any one of claims 1 to 5, wherein said mutation affects one or more amino acid residue(s) selected from the group of residues consisting of the threonine in position 404, the aspartic acid in position 406, the valine in position 452, the lysine in position 506, the glutamine in position 508, and the threonine in position 556 of the wild type Ad2 fiber protein.

10. The modified adenoviral fiber according to any one of claims 1 to 9, wherein said modified adenoviral fiber further comprises at least one additional mutation affecting one or more amino acid residue(s) of said adenoviral fiber interacting with the CAR cellular receptor.

11. The modified adenoviral fiber according to claim 10, wherein said modified adenoviral fiber has an affinity for said CAR cellular receptor and said glycosaminoglycan and/or sialic acid-containing cellular receptor of at least about one order of magnitude less than a wild-type adenoviral fiber.

12. The modified adenoviral fiber according to claim 10 or 11, wherein said additional mutation affects one or more amino acid residue(s) selected from the group consisting of the serine in position 408, the proline in position 409, the arginine in position 412, the lysine in position 417, the lysine in position 420, the tyrosine in position 477, the arginine in position 481, the leucine in position 485, the tyrosine in position 491, the alanine in position 494, the phenylalanine in position 497, the methionine in position 498, the proline in position 499 and the alanine in position 503 of the wild type Ad5 fiber protein as shown in SEQ ID NO : 1.

13. The modified adenoviral fiber according to claim 12, wherein said additional mutation comprises :
    - the substitution of the serine in position 408 by glutamic acid (S408E),
    - the substitution of the proline in position 409 by lysine (P409K),
    - the substitution of the tyrosine in position 477 by alanine (Y477A),
    - the substitution of the leucine in position 485 by lysine (L485K),
    - the substitution of the tyrosine in position 491 by aspartic acid (Y491D),
    - the substitution of the alanine in position 494 by aspartic acid (A494D),
    - the substitution of the phenylalanine in position 497 by aspartic acid (F497D),
    - the substitution of the methionine in position 498 by aspartic acid (M498D),
    - the substitution of the proline in position 499 by glycine (P499G),
    - the substitution of the alanine in position 503 by aspartic acid (A503D), or
    - any combination thereof.

14. The modified adenoviral fiber according to claim 13, wherein said modified adenoviral fiber comprises (i) the substitution of the serine in position 408 by glutamic acid, the substitution of the lysine in position 506 by glutamine and the substitution of the histidine in position 508 by lysine (S408E/ K506Q/H508K) (ii) the substitutiton of the alanine in position 503 by aspartic acid, the substitutiton of the lysine in position 506 by glutamine and the substitutiton of the histidine in position 508 by lysine (A503D/K506Q/H508K), (iii) the substitutiton of the serine in position 408 by glutamic acid and the substitutiton of the serine in position 555 by lysine (S408E/S555K), or (iv) the substitutiton of the alanine in position 503 by aspartic acid and the substitutiton of the serine in position 555 by lysine (A503D/S555K).

15. The modified adenoviral fiber according to any one of claims 1 to 14, wherein said modified adenoviral fiber trimerizes when produced in a eukaryotic host cell.

16. A trimer comprising the modified adenoviral protein of anyone of claims 1 to 15.

17. The trimer according to claim 16, having an affinity for a native glycosaminoglycan and/or sialic acid-containing receptor of at least about one order of magnitude less than a wild type adenoviral fiber trimer.

18. The trimer according to claim 16 or 17, containing a modified adenoviral fiber according to anyone of claims 10 to 15, wherein said trimer further has an affinity for a native CAR cellular receptor of at least about one order of magnitude less than a wild type adenoviral fiber trimer.

19. A DNA fragment or expression vector encoding the modified adenoviral fiber of anyone of claims 1 to 15.

20. An adenoviral particle lacking a wild-type fiber and comprising the trimer of any one of claims 16 to 18.

21. The adenoviral particle of claim 20, further comprising one or more penton base having a mutation affecting at least one native RGD sequence.

22. The adenoviral particle of claim 20 or 21, further comprising a ligand.

23. The adenoviral particle of claim 22, wherein said ligand binds at least one cell-surface anti-ligand other than a native receptor which normally mediates cell attachment and/or uptake of a wild-type adenovirus.

24. The adenoviral particle of claim 23, wherein said cell surface anti-ligand is selected from the group consisting of cell-specific markers, tissue-specific receptors cellular receptors, antigenic peptides, tumor-associated markers, tumor-specific receptors and disease-specific antigens.

25. The adenoviral particle of any one of claims 22 to 24, wherein said ligand is immunologically, chemically or genetically coupled to a viral polypeptide exposed at the surface of said adenoviral particle.

26. The adenoviral particle of claim 25, wherein said viral polypeptide exposed at the surface of said adenoviral particle is selected from the group consisting of penton base, hexon, fiber, protein IX, protein VI and protein IIIa.

27. The adenoviral particle of claim 26, wherein said ligand is genetically inserted in said modified fiber, especially at the C-terminus or within the HI loop.

28. The adenoviral particle of claim 26, wherein said ligand is genetically inserted in the protein pIX, especially at the C-terminus or within the C-terminal portion of said protein pIX.

29. The adenoviral particle of any one of claims 20 to 28, which is an empty capsid.

30. The adenoviral particle of any one of claims 20 to 28, comprising an adenoviral genome.

31. The adenoviral particle of claim 30, wherein said adenoviral genome is replication-defective.

32. The adenoviral particle of claim 30 or 31, wherein said adenoviral genome comprises at least one gene of interest placed under the control of the regulatory elements allowing its expression in a host cell.

33. The adenoviral particle of claim 32, wherein said regulatory elements allowing the expression of said gene of interest are functional within a host cell presenting at its surface an anti-ligand to which said ligand binds.

34. The adenoviral particle of claim 32 or 33, wherein said regulatory elements comprise a promoter selected from the group consisting of tissue-specific promoters and tumor-specific promoters.

35. A process for producing the adenoviral particle according to any one of claims 20 to 34, comprising the steps of :

- Introducing said adenoviral particle or the genome of said adenoviral particle into a suitable cell line,
- Culturing said cell line under suitable conditions so as to allow the production of said adenoviral particle, and
- Recovering the produced adenoviral particle from the culture of said cell line, and
- Optionally purifying said recovered adenoviral particles.

36. The process according to claim 35, wherein said adenoviral particle is replication-defective and said cell line complements at least one defective function of said adenoviral particle.

37. The process of claim 35 or 36, wherein said cell line comprises either in a form integrated into the genome or in episome form a DNA fragment or an expression vector according to claim 19.

38. The process according to claim 37, wherein said cell line is further capable of complementing one or more adenoviral functions selected from the group consisting of the functions encoded by the E1, E2, E4, L1, L2, L3, L4, L5 regions or any combination thereof.

39. The process according to claim 37 or 38, wherein said cell line is produced from the 293 cell line or from the PER C6 cell line.

40. A composition comprising the adenovirus particle according to anyone of claims 20 to 34, or which is produced using the process according to anyone of claims 35 to 39, in combination with a vehicle which is acceptable from a pharmaceutical point of view.

41. The composition of claim 40, wherein said adenovirus particle is conjugated to a lipid or polymer.

42. Use of the adenovirus particle according to anyone of claims 20 to 34, or which is produced using the process according to anyone of claims 35 to 39 or the composition of

claim 40 or 41, for the prepation of a drug intended for the treatment or the prevention of a disease in a human or animal organism by gene therapy.

43. The use according to claim 42, wherein the disease is a cancer, including glioblastoma, sarcoma, melanomas, mastocytoma, carcinomas as well as breast, prostate, testicular, ovarian, cervix, lung, kidney, bladder, liver, colon, rectum, pancreas, stomac, esophagus, larynx, brain, throat, skin, central nervous system, blood, and bone cancers.